ferent European and Latin American countries has been determined in surveys carried out between 1989 and 1997. In some countries – Germany, UK, Italy, Spain, Denmark and Finland – aminoglycoside resistance in Enterobacteriaceae is predominantly caused by gentamicin-modifying enzymes (AAC(3)-I, AAC(3)-II, and/or ANT(2″)-I). However, in other countries – Belgium, France, Greece, Portugal, Turkey, South Africa, Argentina, Chile and Mexico – aminoglycoside resistance is most often caused by an amikacin-modifying enzyme (AAC(6′)-I) either alone or in combination with the above-mentioned gentamicin-modifying enzymes. A correlation between the types of enzymes observed and aminoglycoside usage in these countries has been suggested and will be discussed.

In the treatment of infections caused by resistant organisms, a frequent problem in many intensive care units, the most likely mechanism of resistance to aminoglycosides should play a role in the empiric choice of antibiotics. In those hospitals where gentamicin-modifying enzymes predominate, netilmicin and amikacin may still be effective choices. Where *ACC(6′)-I occurs alone, gentamicin* may still be useful. However, in countries where combinations of resistance mechanisms occur, only isepamicin retains good *in vitro* activity and should be considered as a first choice in situations where aminoglycoside resistance is high.

S42 How do pharmacokinetics influence the choice of aminoglycoside in the critically ill patient?

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Aminoglycosides remain a mainstay of treatment for serious Gram-negative infections.

Following intramuscular administration, aminoglycosides are completely absorbed; they are not metabolized and any drug substance in the plasma and urine is unchanged drug. Anminoglycosides are completely eliminated via the renal route. Doses should therefore be adjusted in patients with renal insufficiency according to the extent of renal impairment.

The area under the plasma concentration curve (AUC) is proportional to the dose of aminoglycoside administered while clearance, volume of distribution at steady state and half-life are independent of dose. After intravenous dosing, the aminoglycoside plasma concentration curve can be best characterized by a tri-exponential curve. The first half-life represents the distribution phase, the second represents the elimination phase, while the g-phase represents the return of the drug to the plasma from deep compartments (i.e. binding in renal tissue).

Isepamicin is a new aminoglycoside which has activity against many bacteria resistant to other aminoglycosides. The pharmacokinetics of isepamicin are uncomplicated and generally similar to those of other aminoglycosides, although evidence suggests that it may have higher peak levels and less tissue accumulation. The g-phase is 34 hours while that of gentamicin and tobramycin is 94 and 96 hours, respectively. Decreased tissue accumulation, implied from these pharmacokinetic data, could be clinically relevant in terms of reduced ototoxicity and renal toxicity, especially in compromised patients.

S43 The Evolution of Dosing Schedules in Aminoglycoside Therapy

P. Tulkens. *B*

No abstract available.

S44 The Rationale for and Use of Aminoglycosides in Combination Therapy

J. Chow. *USA*

No abstract available.

S45 Consensus on the clinical use of aminoglycosides – the Swiss Experience

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Background: Substantial (up to five-fold), poorly understood variations in the use and consumption of aminoglycosides (agly) has been observed among different Swiss hospitals of similar size and patient structure.

Objective: Better understanding of arguments for and against the use of agly for various indications. Swiss consensus for agly recommendations.

Design: *Consensus conference including experts from* all Swiss university hospitals and representative county hospitals.

Topics: Use and consumption of agly; role of agly and optimal schedule for various infections in different target patients; practice of monitoring.

Conclusions: Agly are *highly recommended* (q8h) as part of the standard treatment of 1. endocarditis due to streptococci (MIC of peniG > 0.1 mg/l) or enterococci; 2. the initial 2–3 days of endocarditis due to staphylococci; 3. the febrile neutropenic patient with sepsis; 4. exacerbations of bronchopulmonary infections in cystic fibrosis patients.*Minor recommendations* (OD regimen) are for: 1. shortening the duration of antibiotic combination treatment of endocarditis due to streptococcus viridans (MID of peniG < 0.1 mg/l); 2. combination treatment of the febrile neutropenic patient; 3. the initial 2–3 days of Gram-negative sepsis (with shock); 3. sepsis/meningitis in the newborn (q8h); 4. some infrequent infections such as tularemia, brucellosis, listeria, atypical mycobacteriosis. *Monitoring* of trough levels is highly recommended. In contrast, monitoring of peak levels is not needed in OD regimens in particular.

Bacterial mechanisms for evading cellular host defences

S47 Cell Biology of Phagocytes: Lessons from Mycobacteria

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Mycobacterium tuberculosis survives and replicates within macrophages but the mechanism whereby tubercle bacilli resist killing are incompletely understood. *M. tuberculosis* enter macrophages by receptor-mediated phagocytosis. A remarkable range of different macrophage receptors mediate phagocytosis and/or binding of *M. tuberculosis:* the complement receptors CR1, CR3 and CR4, the macrophage mannose receptor, the Fcg receptor, class A scavenger receptors, phagocyte CD14 molecules, and the surfactant protein A receptor of alveolar macrophages. The survival of certain intracellular pathogens like *S. typhimurium, L. monocytogenes,* and *L. major* within macrophages depends on selective use of a receptor that mediates phagocytosis but not killing. In contrast, evidence from receptor blocking experiments suggests that the intracellular survival and replication of virulent *M. tuberculosis* is independent of the receptor that mediates phagocytosis.

By selectively modulating the fusion-capacity of its phagosome *M. tuberculosis* seems to regulate its vacuole's maturation along the

phagosomal-lysosomal pathway. While recycling of plasma membrane proteins and clearance of endosomal markers from the phagosome are delayed, only low levels of lysosome-associated membrane proteins and cathepsin D are found in the vacuole. In addition, the vesicular proton-ATPase is excluded from the phagosomal membrane, impairing full acidification and thus restricting the hydrolytic activity of the vacuole. However, rather than being fusion-incompetent vacuoles containing mycobacteria are highly selective of the intracellular compartments with which the mix. This is illustrated by the observation that some plasmalemma-derived constituents like glycosphingolipids can readily access mycobacterial vacuoles. Our understanding of the maturation of intracellular compartments will be enhanced by further studies on *M. tuberculosis* containing vacuoles.

S48 The Immunopathogenesis of Chlamydial Infection

M.E. Ward. *UK*

No abstract available.

S49 Molecular and Cellular Mechanisms of *Shigella* Interaction with Epithelial and Phagocytic Cells: An Escape Strategy?

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Invasion of the intestinal barrier by an enteric pathogen such as *Shigella flexneri* encompasses a complex interplay of interactions between epithelial and phagocytic cells. Massive perturbation of the signals that maintain tissue homeostasis and integrity achieves destabilization of the epithelial cohesion, invasion of epithelial and mucosal cells, and eventually tissue destruction. A major factor in this process is expression by *S. flexneri* of an "invasive phenotype" related to its capacity, upon contact with target cells, to release via a type III secretory apparatus a set of Ipa (invasion) proteins. Ipas can trigger entry of the pathogen into epithelial cells via a macropinocytic event that involves massive rearrangement of the cell cytoskeleton.

Ipas can also trigger macrophage apoptotic death via direct interaction with the cysteine protease ICE, thus killing defense cells and achieving release of IL-1β which initiates inflammation. The likely scheme that has emerged from our *in vitro* and *in vivo* experiments is the following: bacteria translocate through the epithelial barrier via M cells of the follicular associated epithelium covering the lymph nodes located within the colonic mucosa. Apoptotic death of macrophage allows bacterial survival, entry into epithelial cells via their basal pole, but also triggers early inflammation which destabilizes the epithelial structure and facilitates further bacterial entry.

Once intracellular, bacteria escape into the cytoplasm and move from cell to cell via an actin-dependent process. This overall process causes the tissue destruction which is characteristic of shigellosis.

S50 *Listeria monocytogenes* as a Model for Studying the Behaviour of Intracellular Bacteria

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Listeria monocytogenes, a Gram-positive, facultative intracellular bacterium, can cause systemic infections in pregnant women, neonates, and immuno-compromised people with symptoms such as septicaemia and encephalo-meningitis. These bacteria enter phagocytes as well as non-phagocytic host cells and replicate in the cytosol of these cells after escape from the phagosome. In the cytosolic compartment *L. monocytogenes* polymerises actin which allows intra- and intercellular movement of the bacteria. All virulent *L. monocytogenes* strains possess a gene cluster flanked by the house keeping genes *prs* (encoding phosphoribosyl-pyrophosphate synthetase) and *ld* (encoding lactate dehydrogenase) which consists of six virulence genes. Their products comprise two phospholipases C, listeriolysin, a metalloprotease, the actin nucleator ActA and the transcriptional activator PrfA. This latter regulatory protein is essential for the expression of all six clustered virulence genes and the *inl* genes. The *inl* genes encode leucine-rich repeat (Lrr) proteins that fall into two classes: the large Inl proteins are cell-associated and are involved in the internalization of *L. monocytogenes* into non-professional phagocytic host cells while the small Inls are secretory proteins which are synthesised preferentially within the host cells. The differential expression of the virulence genes is accomplished by the interaction of PrfA with other bacterial factors which is influenced by environmental parameters.

Some of the listerial virulence factors are predominantly expressed when the bacteria replicate outside the host cells whereas others are mainly expressed within the intracellular compartments. Depending on the site of synthesis these virulence factors trigger specific host cell responses. Host cell responses have been studied in our laboratory mainly for the interaction of *L. monocytogenes* with macrophages which represent major target cells in *L. monocytogenes* infection. Their reactions are crucial for the progress of a *L. monocytogenes* infection.

Tracking methicillin-resistant Staphylococci

S51 Clonality and Evolution of Methicillin Resistant Staphylococcus Aureus: Application of Molecular Typing Techniques for Epidemiologically Valid Detection of Genetic Polymorphisms

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No abstract available.

S52 Tracking and Managing Nosocomial MRSA Infections

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Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be an important nosocomial pathogen. The prevalence of MRSA in hospitals varies considerably by geographic area, hospital size and possibly by hospital type. The percent of *S. aureus* isolates that are MRSA ranges from <5% in some hospitals to more than 60% in others. The incidence of ongoing nosocomial transmission of MRSA is best expressed as the number of new nosocomial MRSA cases/1000 patient-days. Minimizing nosocomial transmission of MRSA requires prompt detection and reporting of MRSA cases by the laboratory, appropriate isolation and barrier precautions, surveillance cultures on wards where case clustering occurs, and prompt isolation of known cases upon readmission to the hospital. Frequent use of gloves by personnel and improved compliance with hand hygiene are strategies that deserve increased emphasis. Eradicating MRSA nasal carriage in patients and in personnel implicated in transmission of MRSA can contribute to control of MRSA, but the indications for decolonization therapy remain controversial. Currently, intranasal mupirocin is the most effective regimen for eradicating nasal carriage. Widescale use in hospitals and prolonged application of mupirocin to